MicroRNAs: Suggested role in pituitary adenoma pathogenesis

M.R. Gadelha1, L. Kasuki1, J. Dénes2, G. Trivellini2, and M. Korbonits2

1Division of Endocrinology, Clementino Fraga Filho University Hospital, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil; 2Centre for Endocrinology, Barts and the London School of Medicine, Queen Mary University of London, UK

ABSTRACT. MicroRNAs (miRNAs) are small non-coding RNA molecules that represent a major class of molecular regulators. miRNAs have been implicated in the pathogenesis of several human tumors, including pituitary adenomas. Altered expression of miRNAs has been described in pituitary adenomas, and specific miRNA signatures are related to clinical and therapeutic characteristics of the tumors. The data suggest that miRNAs influence various genes known to be associated with the pathogenesis of pituitary adenomas and in this review we summarize these currently available studies focusing on miRNAs in pituitary adenomas.

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Short Review

MicroRNAs – Definition, Biosynthesis and Binding to Target mRNAs

MicroRNAs (miRNAs) are small [approximately 19-25 nucleotides (nt)] non-coding RNA molecules involved in the post-transcriptional regulation of gene expression. They constitute a major class of molecular regulators, regulating about 30% of human genes (1, 2). They were first described in the nematode Caenorhabditis elegans in 1993 (3), with let-7 being the first miRNA described in the human species in 2000 (4). miRNAs are found in the genome of animals, plants, and protozoa (5). Since the first report, more than 1500 human miRNAs have been described (6). miRNA sequences are dispersed throughout the genome and are classified as intergenic (between genes) or intronic (embedded within a gene) (7). Intergenic miRNAs are expressed via their own promoter, while intronic miRNAs can be expressed either via the host gene promoter transcribed by the RNA Polymerase II enzyme or via their own promoter transcribed by RNA Polymerase III (7).

The first step in miRNA biosynthesis is transcription of the miRNA sequence by RNA polymerase II or III to produce a long miRNA precursor called primary miRNA (pri-miRNA) (Fig. 1). The pri-miRNA may contain either a single or a cluster of distinct miRNAs and may be from approximately 200 nt to several thousand nt in length. The pri-miRNA has a characteristic stem-loop structure (Fig. 1). The stem-loop structure is recognized and cleaved by a heterodimer consisting of the cellular RNase III enzyme Drosha and a cofactor called double-stranded RNA binding protein Pasha (also known as DGCR8), which is essential for Drosha activity. This cleavage liberates an approximately 60 nucleotides (nt) hairpin looped-structured RNA, called pre-miRNA. All these described steps occur in the nucleus. The next step is nuclear export of the pre-miRNA by exportin 5 (8). After reaching the cytoplasm, the pre-miRNA binds to a second cellular RNase III enzyme called Dicer. Dicer binds the overhang at the base of the pre-miRNA hairpin and removes the terminal loop, generating a 19-25 nt duplex miRNA intermediate (miRNA – miRNA duplex). This duplex miRNA is incorporated into a complex called RNA-induced silencing complex (RISC). The RISC composition is not completely known, but a key component is an argonaute protein. Then, one strand is retained and becomes the mature miRNA, while the other strand, called miRNA*, is discarded (2).

Usually, the miRNA binds to a region located in the 3′ untranslated region (3′UTR) of the target mRNA. When a miRNA binds to perfectly complementary base pairs in the mRNA strand, degradation of the mRNA by RISC occurs (2). However, more commonly, a miRNA binds to a partially complementary mRNA sequence and this induces translational repression of the target mRNA or the recently discovered miRNA-mediated mRNA deadenylation (Fig. 1) (2, 9). In a few cases, an interaction between a miRNA and its target mRNA has been shown in the open reading frame of the mRNA (10, 11).

Generally, miRNA:mRNA duplexes consist of a 5′ end “seed” region, a central loop region, and a 3′ end tail region. The major determinant of the interaction between a miRNA and its mRNA targets corresponds to the “seed” region of the miRNA (from 6 to 8 nt at position 1-8 at its 5′ end), which pairs with mRNA complementary sequences (12). The binding at the “seed” region can be canonical, when there is 7-8 nt match, or non-canonical when matching is less perfect (12). The central loop has also been shown to be another important factor in miRNA functioning (13), and supplementary base pairing involving the 3′ portion of the miRNA can enhance binding specificity and affinity (12). Moreover, the secondary structure, as well as the whole 3′UTR sequence, may contribute to miRNA function (14-16). In addition, the presence of RNA-binding proteins in the 3′UTR could physically prevent the interaction of a miRNA with nearby target site (17).
miRNAs IN HUMAN NEOPLASIAS

miRNAs have been implicated in many cellular processes, including cell proliferation, apoptosis, cell adhesion and metabolism, and have a role in many developmental processes, including stem cell and germline maintenance, development, and differentiation (6). Thus, alterations in miRNAs expression can potentially be involved in the development of human neoplasias. Indeed, miRNAs are aberrantly expressed for example in liver, pancreas, esophageal, stomach, colon, hematopoietic, ovarian, breast, prostate, thyroid, testicular, and brain cancers (6, 18, 19).

miRNAs can act either as activators or inhibitors of carcinogenesis, and are called oncomiRs or tumor suppressor miRNAs accordingly (4). An example of tumor suppressor miRNA is let-7, whose reduced expression is associated with metastatic disease and poorer prognosis in lung cancer (20). In contrast, miR-21 acts as an oncomiR and is overexpressed in many human neoplasias, with its knockdown being associated with increased apoptotic activity (4).

Pituitary blastoma is a recently described tumor of the pituitary composed of primitive Rathke-type epithelium and adenohypophysial cells of folliculostellate and secretory type (21). Recently, Wildi-Runge et al. described a 9-month male infant with pituitary blastoma and Cushing’s syndrome and a family history of pleuropulmonary blastoma and a cystic nephroma in 2.7 yr male second cousin, whose grandmother had renal cysts and an ovarian tumor (22). Genetic analysis revealed a germline heterozygous nonsense mutation in the gene DICER1 as a possible cause of this complex syndrome (22). As previously mentioned, DICER1 is one of the enzymes involved in miRNAs synthesis. Recently, Scheithauer et al. reported 2 additional cases of pituitary blastoma, all in infants and ACTH-producing (23). The genetic cause of these cases is to be reported soon.

miRNAs IN PITUITARY ADENOMAS

Pituitary adenomas are usually benign monoclonal sporadic tumors (24). Rarely, they can be part of a familial disease, like multiple endocrine neoplasia type 1 (MEN1) or 4 (MEN4) and familial isolated pituitary adenoma (FI-PA) syndromes (25-27). Despite being a common cause of intracranial tumors (approximately 10-15% of the cases), the pathogenesis of the vast majority of the cases is currently not completely known (28). As in other human neoplasias, there is an increasing interest in the study of miRNAs in pituitary adenomas and carcinomas. miRNAs have been described to be associated with tumor type, characteristics (size, invasion) and response to therapy (Table 1) (29-34). They have also been involved in the regulation of several genes suggested to be associated with the pathogenesis of pituitary adenomas (Table 2). Bottini et al. were the first to describe the expression of...